Acta Scientific Cancer Biology

Volume 1 Issue 1 June 2017

Editorial

Mutation or Methylation?

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Received: June 05, 2017; **Published:** July 03, 2017

Among the alterations involved in cancer, modifications in genes related to the cell cycle, proliferation, and apoptosis pathways are common. The majority of work evaluates germline or somatic genetic mutations which occur directly in the DNA sequence, while far less work has been done to analyse changes that do not modify DNA sequences themselves but rather, examine dysregulated epigenetic factors, such as modifications in histones, microRNAs, and DNA methylation.

DNA methylation plays several critical roles in gene regulatory processes. One clear example of the importance of methylation is that of the breast cancer 1/2 (*BRCA1/2*) genes. These tumour suppressor genes play an essential part in the homologous recombination (HR) system. *BRCA1/2* are linked to development of ovarian and breast cancer, and are associated with a high risk of developing other cancers, including prostate, pancreatic, and endometrial cancers. At the functional level, dysregulated *BRCA1/2* promotor methylation has the same effect as DNA mutations in these genes, given that either of these alterations can produce a disease phenotype in patients harbouring these modifications. This also occurs in other DNA repair genes, for example, loss of *MGMT* expression caused by promoter hypermethylation has been found in pancreatic tumours [1]. Similarly, methylation of the *BIN1* gene promoter CpG island reduces its expression and is associated with breast and prostate cancers [2]. Likewise, comparison of normal versus cancerous breast tissue identified 10 hypermethylated genes in the cancerous samples, which are involved in cell cycle and DNA repair (*BRCA1, P16* and *P21*), invasion and metastasis (*CST6* and *TIMP3*), cell proliferation (*ESRb)*, signal transduction (*APC, BIN1,* and *BMP6*) and cell detoxification (*GSTP1*). Thus, reactivating these genes by inhibiting DNA hypermethylation is an attractive avenue for the development of novel therapeutics [3].

Shan and collaborators, examined the promoter methylation of six genes (*SFN, P16, hMLH1, HOXD13*, *PCDHGB7*, and *RASSF1a*) in circulating free DNA extracted from serum from breast cancer patients, patients with benign breast diseases, and healthy women. Their data suggest that the epigenetic markers identifiable from serum could potentially be used to diagnose breast cancer [4]. Similarly, hypermethylation-mediated *PDLIM4* repression may be a potential biomarker in prostate cancer [5]. Other studies have shown that variable gene methylation levels can be useful in differentiating several tumour subgroups. For example, the methylation levels of the DNA repair genes *hMLH1, hMSH2, MGMT*, and *BRCA1* can be used to distinguish between basal-like and non-basal-like breast cancers [6]. Aberrant methylation levels of *ABCB1, FOXC1, GSTP1, PPP2R2B*, and *RASSF1A* in breast cancer have also been correlated with clinical-pathological parameters such as age or cancer TNM stage (I-IV). This suggests that changes in methylation levels is an early event and which may also be important in progression to later stages of breast cancer [7]. Importantly, the DNA methylation status of the *GSTP1, FOXC1*, and *ABCB1* gene promoters has been correlated with breast cancer survival [8]. Moreover, the downregulation of DNA mismatch-repair proteins has also been related to multicellular resistance, especially to alkylating agents [9].

Cancers with dysfunctional DNA-repair mechanisms are especially sensitive to PARP inhibitors. Moreover, this treatment can result in synthetic lethality and so these drugs are now being evaluated in several clinical trials. Currently, only patients with germline or somatic mutations are treated with PARP inhibitors or platinum-based chemotherapy [10]. However, it is likely that other patients with HR-deficient tumours generated by epigenetic modifications could also benefit from such treatments. Indeed, the *BRCA1* promoter is frequently found to be hypermethylated in ovarian and breast cancer [11,12], but mutations in other HR genes such as *RAD51*, *ATM*, or *PALB2* [13-16] have also been related to uterine serous carcinoma, lung, breast, and skin cancer.

Thus, aberrant gene-promoter methylation is common in many DNA repair genes, and this may have important implications in treatment sensitivity and resistance [17]. For example, chemotherapy resistance has been related to loss of *BRCA1* promoter methylation [18]. Likewise, methylation of *MGMT*, a gene involved in direct-reversal DNA repair, is correlated with a poor prognosis in gliomas and colorectal and gastric cancers, and is a marker for procarbazine sensitivity [19-21]. Similarly, *ERCC1* promoter methylation is implicated in nucleotide excision repair in glioma cells

sensitised to cisplatin. In ovarian cancer, modifications in the HR system genes *BRCA1* and *FANCF*, resulted in an altered response to cisplatin while the response to PARP inhibitors is impaired in the presence of *BRCA1* alterations in ovarian, non-small cell lung cancer (NSCLC), and gastric cancers [22-24]. The *MLH1-2* gene, involved in mismatch repair, has been related to carboplatin, cisplatin, and epirubicin resistance in several cancers [22,25]. Likewise, epigenetic alterations in *WNR*, implicated in base excision repair, are associated with sensitivity to irinotecan in NSCLC, colorectal, gastric, prostate, breast, and thyroid cancers [26].

Besides being involved in responses to specific treatments, the methylation of DNA repair genes has also been associated with cancer risk and can be used to diagnose and classify tumours. In addition, these types of alterations may also be useful as prognosis and predictor markers, and perhaps even as future therapeutic targets. In summary, the examples described above should help to highlight the importance of continued and intensified epigenetic research and the exhaustive analysis of patient samples in order to identify genes which may be epigenetically altered in disease states.

In conclusion, the answer to the title question is easy: changes in methylation can be just as relevant as mutations if they occur in a DNA area which results in gene silencing. Therefore, we must pay close attention to these modifications and not neglect them. The most important potential outcome of such research is the possible use of these alterations to discern the patient subgroups who will respond differently to specific DNA-damage treatments.

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Volume 1 Issue 1 June 2017